NAPM

NATIONAL ASSOCIATION OF PHARMACEUTICAL MANUFACTURERS

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August 25, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

**RE:** Docket No. 99D-0529 - Guidance for Industry: Changes to an Approved NDA or ANDA

The National Association of Pharmaceutical Manufacturers (NAPM) appreciates the opportunity to comment on the document, " Guidance for Industry: Changes to an Approved NDA or ANDA" [Docket No. 99D-0529]. These comments represent the consensus of leading manufacturers of generic drug products.

We wish to compliment the Agency in producing a document that covers most issues regarding the reporting of postapproval changes for approved drug products. This document is quite complete and we are very pleased that the Agency has considered reducing industry's burden for filing extensive reports concerning postapproval changes. Our recommended changes to this document are intended to clarify the document and not rewrite it.

NAPM is the national trade organization representing manufacturers, distributors and repackagers of generic multisource prescription drugs, OTC drugs, dietary supplements and veterinary drugs. The organization prides itself in serving the needs of its members and has been heavily involved in legislative, legal, regulatory and technical issues.

We thank you for the opportunity to submit our comments. We hope that our comments are clear and welcome any questions that you may have.

Sincerely,

Leon Shargel

Leon Shargel, Ph.D.
Vice President and Technical Director

cc: Nancy Sager

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99D-0529

**GUIDANCE FOR INDUSTRY:**
**CHANGES TO AN APPROVED NDA OR ANDA**
**[DOCKET NO. 99D-0529]**

This document is quite complete and covers most issues regarding the reporting of postapproval changes for approved drug products. However, we have several comments listed below that have been recommended by our members.

**Specific Comments:**

p. 3, lines 54-56

*Requests for expedited review based on extraordinary hardship should be reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.*

Comment:

NAPM agrees with intent of this sentence. However, NAPM would like to include the loss of a primary raw material supplier as an example of another possible event that should require expedited review based on extraordinary hardship.

NAPM would like to modify the above sentence (lines 54-56) to read:

"Requests for expedited review based on extraordinary hardship should be reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events **(e.g., loss of a primary raw material supplier)** that could not be reasonably foreseen and for which the applicant could not plan."

p. 3, lines 57-73

This paragraph discusses **Supplement-Changes Being Effected in 30 days** and **Supplement-Changes Being Effected**.

NAPM requests the agency to provide more clarity in describing the differences in a "moderate change" that would trigger a *Supplement -CBE in 30 days* versus a *Supplement-CBE.*. The agency should give some specific examples that would fit into each of these categories.

pp. 4-5, lines 106-114

IV. Assessing the Effect of Manufacturing Changes
A. Validate the Effects of the Change

Comment:

NAPM does not feel that validation data needs to be sent to the agency. We consider that all the validation data described in this section is cGMP validation data and the agency should not have to critique the cGMP validation data. The cGMP validation data is generally reviewed by the District as part of the pre-approval data.

NAPM feels that the agency needs to better define the term, "non-cGMP validation" data. We also need clarification as to the requirements for non-cGMP validation in terms of the number of batches, batch size, packaging, etc.

pp. 5-6, lines 130-148

IV. A. 1. Additional Testing

Comment:

A minor change should not require all these additional types of testing since the minor change has minimal adverse effect on the strength, quality, purity, or potency of the drug products. The drug product should meet the approved specifications after the change.

p. 7, lines 187-189

*Changes in the qualitative or quantitative formulation including inactive ingredients, as provided in the approved application are considered major changes and should be filed in a prior approval supplement, unless exempted by regulation or guidance (21 CFR 314.70(b)(2)(I)).*

Comment:

NAPM feels that the SUPAC guidance documents should be used for quantitative changes. We suggest that the above sentence should be changed to read:

"Changes in the qualitative **formulation** or quantitative formulation **outside of SUPAC guidelines** including inactive ingredients, as provided in the approved application are considered major changes and should be filed in a prior approval supplement, unless exempted by regulation or guidance (21 CFR 314.70(b)(2)(I))."

p. 9, lines 262-268 Section VI. B. 4.

Comment:

NAPM feels as long as the same equipment, processing, etc is used for the manufacture of complex dosage forms, the reporting requirement for complex dosage forms should be a *supplement-changes being effected in 30 days* rather than a *prior-approval supplement.* Complex dosage forms should not require extraordinary reporting compared to immediate release dosage forms.

p. 10, lines 292-293 Section VI. C. 1. c.

Comment:

Provided that the approved packaging conditions have not changed, a move to a site on a different campus for the primary packaging of any drug product that is not listed as a major change should be considered a minor change and reported in an annual report.

p. 10, lines 294-300 Section VI. C. 1. d.

Comment:

NAPM feels that a move to an approved facility using the same validated testing method does not affect the quality and safety of the product. *A Supplement-Changes Being Effected* should be reported rather than a *Supplement-Changes Being Effected in 30 Days* .

p. 12, lines 294-300 Section VII. B. 1.

Comment:

A change in embossing, debossing or engraving on a modified release solid oral dosage form should be considered a minor change and reported in an annual report as long as dissolution/release specifications are met and no other changes have been made.

p. 14, lines 294-300 Section VII. B. 7.

Comment:

Reprocessing may be minor (e.g., adjustment of pH), moderate or major depending upon the potential effect on the identity, strength, quality, purity or potency of the product. The reporting requirements for reprocessing should be based on whether the potential effect on the drug product is minor, moderate or major.

p. 16, lines 488-489

4. *To add a code imprint by embossing, debossing, or engraving on a solid dosage form drug product other than a modified release dosage form.*

Comment:

Complex dosage forms should not require extraordinary reporting compared to immediate release dosage forms. As mentioned above (under p. 12, lines 294-300 Section VII. B. 1.), a change in embossing, debossing or engraving on a modified release solid oral dosage form should be considered a minor change and reported in an annual report as long as dissolution/release specifications are met and no other changes have been made.

This sentence should be changed to read:

"To add a code imprint by embossing, debossing, or engraving on a solid dosage form drug product ~~other than~~ **including** a modified release dosage form."

p. 17, lines 517

Comment:

Relaxing an in-process specification if within compendial limits and keeping the same finished product specifications would not affect the identity, strength, quality, purity or potency of the product. This is a minor change that should be reported in an annual report.

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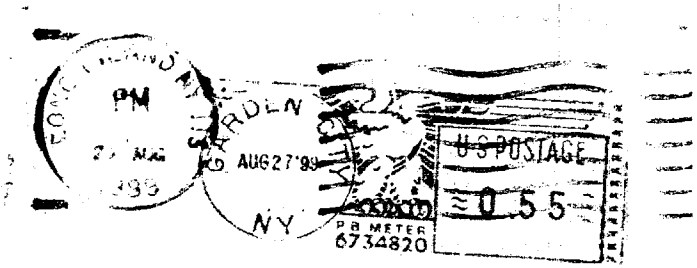


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